HFA - 305, Document Control Unit

DATE OF APPROVAL LETTER: FEB - 8 2002

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 140-890

EXCENEL® RTU Sterile Suspension
A brand of ceftiofur hydrochloride sterile suspension

"For the treatment of acute metritis (0-14 days post-partum) in cattle"

SPONSORED BY:

PHARMACIA & UPJOHN

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I. GENERAL INFORMATION

NADA Number:	140-890
Sponsor:	Pharmacia & Upjohn Company 7000 Portage Rd. Kalamazoo, MI 49001
Established Name:	ceftiofur hydrochloride
Proprietary Name:	EXCENEL® RTU Sterile Suspension
Marketing Status:	This is a prescription product and will include the caution statement as follows: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian
Effect of this Supplement:	This supplement provides a new indication, within the currently approved dose and duration, for use of ceftiofur hydrochloride sterile suspension (EXCENEL® RTU Sterile Suspension) in cattle, for the treatment of acute metritis (0-14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.

II. INDICATIONS FOR USE

For the treatment of bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia* spp. (*Pasteurella haemolytica), Pasteurella multocida* and *Haemophilus somnus*, for the treatment of acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*, and for the treatment of acute metritis (0-14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.

III. DOSAGE

A. *Dosage Form:* Sterile Suspension available in 100 mL vials, each mL contains ceftiofur hydrochloride equivalent to 50 mg ceftiofur.

B. *Route of Administration:* Administered by either intramuscular or subcutaneous injection in cattle.

C. *Recommended dosage:* For acute metritis administer at a dose of 1.0 mg ceftiofur equivalents (CE)/lb (2.2 mg CE/Kg) body weight (BW), 2 mL/ 100 lb BW. Administer at 24-hour intervals for a total of five consecutive days.

IV. EFFECTIVENESS

Data from the following multi-location clinical effectiveness study demonstrate that EXCENEL® RTU Sterile Suspension is effective for the treatment of acute metritis (0 to 14 day post-partum) associated with bacterial organisms sensitive to ceftiofur.

1. Objective: To evaluate under clinical field conditions, effectiveness of ceftiofur hydrochloride sterile suspension administered parenterally at dosages of 0.5 or 1.0 mg CE/lb BW (1.1 or 2.2 mg CE/kg BW) for 5 consecutive days for the treatment of acute post-partum metritis in dairy cows. Ceftiofur hydrochloride is approved for the treatment of bovine respiratory disease and interdigital necrobacillosis (foot rot, pododermatitis) at these dosages.

2. Study Investigators:
Paul Busman, DVM, Coopersville, MI; Steve Carlson, DVM, Tulare, CA; Phillip Jardon, DVM, Visalia, CA; Alfred Harper, DVM, Dublin, TX; Art Sherman, DVM, Geneva, NY; Tony Wiseley, DVM, Perry, NY; Gerard Koenig, DVM, Corcoran, CA; Carlos Risco, DVM, Gainesville, FL.

3. General Design:

   a. Experimental animals: Lactating dairy cows (N = 406) at eight commercial dairies were enrolled that met the following criteria: less than 15 days post-partum, rectal temperature ≥ 103°F (39.5°C), a fetid vaginal/uterine discharge, and no clinical signs of other diseases of the respiratory or digestive tracts detected during a physical examination.

   b. Dosage form: Ceftiofur hydrochloride sterile suspension (50 mg CE/mL), a ready to use formulation (EXCENEL® RTU Sterile Suspension). The control animals were administered sterile saline.

   c. Experimental Design: As cows were found to be eligible for inclusion, they were randomly assigned in blocks to one of three groups: control (sterile saline for injection) or ceftiofur hydrochloride at 0.5 mg or 1.0 mg CE/lb BW (1.1 or 2.2 mg CE/kg BW). All treatments were administered by either subcutaneous or intramuscular injection for 5 consecutive days. Rectal temperature and vaginal discharge were evaluated 6, 10 and 14 days after the initial treatment. Cows that had not been administered additional antimicrobial therapy (escape therapy) and with rectal temperature less than 103°F (39.5°C) and without fetid discharge were defined as cured. Cows

administered additional antimicrobial therapy or with rectal temperature ≥ 103°F (39.5°C) or with a fetid discharge were defined as failed to cure.

d. Statistical Analyses: Of the 406 cows enrolled into the study 30 were removed completely from statistical analyses because they did not fulfill the study requirements (deviations to the protocol). Of the remaining 376 cows, 15 cows either had an observation missing or violated the protocol; therefore, there were 361 cows included in the analyses for cure rates on Day 14; 116, 124 and 121 animals in the saline, 0.5 mg, and 1.0 mg CE/lb BW treatment groups, respectively. The cure rates for each of the ceftiofur treatment groups were compared against the control using the generalized linear mixed model. Rectal temperatures were statistically analyzed at four time periods/points: over the first five days of the study (during treatment); on Day 6; on Day 10; and on Day 14.

5. Results: On Day 14 the 1.0 mg CE/lb BW treatment group had the highest cure rate (77%), followed by the 0.5 mg CE/lb BW treatment group, and the control group (65% and 62%, respectively). The cure rate for the 1.0 mg CE/lb BW treatment group was significantly higher than that of the control group on Day 14 (p=0.010). No difference was detected between the 0.5 mg CE/lb BW treatment group and the control group (p=0.295).

6. Conclusions: The results of this study demonstrate that ceftiofur hydrochloride administered daily for five consecutive days at a dose of 1.0 mg ceftiofur equivalents/lb BW (2.2 mg/kg BW) is an effective treatment for acute metritis (0-14 days post-partum) in cattle.

CLINICAL MICROBIOLOGICAL DATA:

A summary of updated MIC data for swine and cattle pathogens is presented in tabular format in the labeling for EXCENEL® RTU Sterile Suspension. This format is similar to that used for NAXCEL® Sterile Powder (See Supplemental Approval; NADA 140-338, dated July 6, 2000).

V. ANIMAL SAFETY

Ceftiofur hydrochloride sterile suspension was approved previously (NADA 140-890. April 26, 1996) for administration to cattle at dosages of 0.5 to 1.0 mg ceftiofur equivalents per pound body weight (1.1 to 2.2 mg CE/kg BW) for up to five consecutive days for the treatment of bacterial respiratory disease and acute interdigital necrobacillosis (foot rot). Because the dose used for acute post-partum metritis falls within the previously approved dosage regimen, data on file in NADA 140-890 provide sufficient evidence of animal safety for this dosing regimen. Therefore, no additional studies were required for this supplemental application.

VI. HUMAN SAFETY

Ceftiofur hydrochloride was approved previously (NADA 140-890, April 26, 1996) for administration to cattle, including dairy cows, at dosages of 0.5 to 1.0 mg ceftiofur equivalents per pound body weight (1.1 to 2.2 mg CE/kg BW) for up to five consecutive days for the treatment of bacterial respiratory disease and acute interdigital necrobacillosis (foot rot). Because the dose for treatment of acute post-partum metritis falls within the previously approved dosage regimen, data on file in NADA 140-890 provide sufficient evidence of human food safety for this dosing regimen. Therefore, no additional toxicology or residue studies were required for this supplemental application.

VIII. AGENCY CONCLUSIONS

The data submitted in support of this supplemental application satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations to enable FDA to revise 21 CFR 522.314 to provide for the safe and effective use of EXCENEL® RTU Sterile Suspension for the treatment of acute metritis (0-14 days post-partum) associated with bacterial organisms susceptible to ceftiofur in cattle.

The product remains a prescription drug for safe and effective use by or on the order of a licensed veterinarian.

In accordance with 21 CFR 514.106(b)(2)(v), this is a Category II change which did not require a reevaluation of the human food and target animal safety data in the parent application.

Under Section 512 (c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act, this approval for food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, any studies of animal safety, or, in the case of food producing animals, human food safety studies (other than bioequivalence or residue studies) required for the approval of the supplement and conducted or sponsored by the applicant. The THREE years of marketing exclusivity applies only to the new indication for which the supplemental application is approved.

EXCENEL® RTU Sterile Suspension is under patent numbers U.S. 4,902,683 expiring February 20, 2007, and U.S. 5,736,151 expiring April 7, 2015.

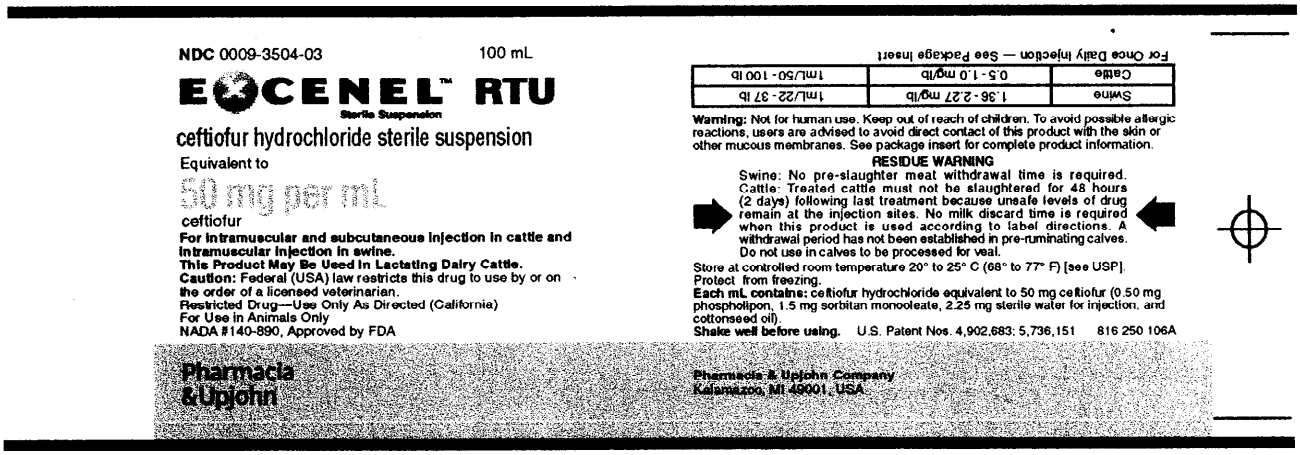
IX. APPROVED PRODUCT LABELING

A copy of the facsimile labeling, including the package insert, is attached to this document.

Copies of applicable labeling may be obtained by writing to:

Freedom of Information Staff (HFI-35)
Food and Drug Administration, Room 12A16
5600 Fisher's Lane
Rockville, Maryland 20857

Supplement to NADA 140-890
EXCENEL® RTU Sterile Suspension



NDC 0009-3504-03 100 mL

EXCENEL™ RTU
Sterile Suspension

ceftiofur hydrochloride sterile suspension

Equivalent to

50 mg per mL

ceftiofur

For intramuscular and subcutaneous injection in cattle and intramuscular injection in swine.
This Product May Be Used in Lactating Dairy Cattle.
Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.
Restricted Drug—Use Only As Directed (California)
For Use in Animals Only
NADA #140-890, Approved by FDA

Pharmacia & Upjohn

Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

For Once Daily Injection — See Package Insert

Swine	Cattle
1.36 - 2.27 mg/lb	0.5 - 1.0 mg/lb
1mL/22 - 37 lb	1mL/50 - 100 lb

Warning: Not for human use. Keep out of reach of children. To avoid possible allergic reactions, users are advised to avoid direct contact of this product with the skin or other mucous membranes. See package insert for complete product information.

RESIDUE WARNING

Swine: No pre-slaughter meat withdrawal time is required.
Cattle: Treated cattle must not be slaughtered for 48 hours (2 days) following last treatment because unsafe levels of drug remain at the injection sites. No milk discard time is required when this product is used according to label directions. A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal.

Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP].
Protect from freezing.
Each mL contains: ceftiofur hydrochloride equivalent to 50 mg ceftiofur (0.50 mg phospholipon, 1.5 mg sorbitan monooleate, 2.25 mg sterile water for injection, and cottonseed oil).
Shake well before using. U.S. Patent Nos. 4,902,683; 5,736,151 816 250 106A

Excenel® RTU

Pharmacia &Upjohn

brand of ceftiofur hydrochloride sterile suspension

For intramuscular and subcutaneous use in cattle and intramuscular use in swine. This product may be used in lactating dairy cattle.

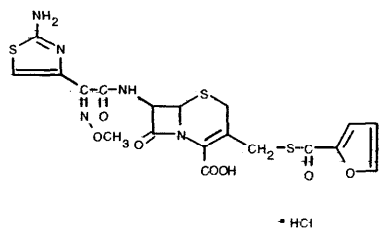
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

EXCENEL RTU Sterile Suspension is a ready to use formulation that contains the hydrochloride salt of ceftiofur, which is a broad spectrum cephalosporin antibiotic.

Each mL of this ready-to-use sterile suspension contains ceftiofur hydrochloride equivalent to 50 mg ceftiofur, 0.50 mg phospholipon, 1.5 mg sorbitan monooleate, 2.25 mg sterile water for injection, and cottonseed oil.

Structure:



• HCl

Figure 1

Chemical Name of Ceftiofur Hydrochloride: 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[(2-furanylcarbonyl) thio]methyl]-8-oxo-,hydrochloride salt [6R-[6α,7β(Z)]]-

CLINICAL PHARMACOLOGY

Swine: Ceftiofur administered as either ceftiofur sodium or ceftiofur hydrochloride is metabolized rapidly to desfuroylceftiofur, the primary metabolite. Administration of ceftiofur to swine as either the sodium or hydrochloride salt provides effective concentrations of ceftiofur and desfuroylceftiofur metabolites in plasma above the MIC_{90} for the labeled pathogens: *Actinobacillus pleuropneumoniae, Pasteurella multocida, Streptococcus suis* and *Salmonella choleraesuis* for the 24 hour (h) period between the dosing intervals. The MIC_{90} for *Salmonella choleraesuis* (1.0 µg/mL) is higher than the other three pathogens and plasma concentrations exceed this value for the entire dosing interval only after the 2.27 mg/lb (5.0 mg/kg) body weight (BW) dose.

Comparative Bioavailability Summary

Comparable plasma concentrations of ceftiofur administered as ceftiofur hydrochloride sterile suspension (EXCENEL RTU Sterile Suspension) or ceftiofur sodium sterile solution (NAXCEL® Sterile Powder) were demonstrated after intramuscular administration of 2.27 mg ceftiofur equivalents/lb (5.0 mg/kg) BW. See Table 1 and Figure 2.

Table 1. Swine plasma concentrations and related parameters* of ceftiofur and desfuroylceftiofur metabolites after EXCENEL RTU Sterile Suspension (ceftiofur hydrochloride sterile suspension, 50 mg/mL) or NAXCEL Sterile Powder (ceftiofur sodium sterile powder, 50 mg/mL) administered at 2.27 mg/lb ceftiofur equivalents/lb (5.0 mg/kg) BW IM.

	Ceftiofur hydrochloride	Ceftiofur sodium
C_{max} µg/mL:	26.1 ± 5.02	29.2 ± 5.01
t_{max} h:	0.66 – 2.0 (range)	0.33 – 2.0 (range)
$AUC_{0\text{-}LOQ}$ µg•h/mL:	321 ± 50.2	314 ± 55.1
$t_{1/2}$ h:	16.2 ± 1.55	14.0 ± 1.23
$C_{24\ h}$ µg/mL:	3.45 ± 0.431	3.53 ± 0.791
$C_{72\ h}$ µg/mL:	0.518 ± 0.126	0.407 ± 0.0675
$t_{>0.2}$ h:	93.8 ± 7.98	85.0 ± 7.71

Definitions:

C_{max} – maximum plasma concentration in µg/mL.

t_{max} – the time after initial injection to when C_{max} occurs, measured in hours.

$AUC_{0\text{-}LOQ}$ – the area under the plasma concentration vs. time curve from time of injection to the limit of quantitation of the assay (0.15 µg/mL).

$t_{1/2}$ – the plasma half life of the drug in hours.

$C_{24\ h}$ – the concentration of drug at 24 h after administration.

$C_{72\ h}$ – the concentration of drug at 72 h after administration.

$t_{>0.2}$ – the time (in hours) plasma concentrations remain above 0.2 µg/mL.

* Due to significant period effect and significant sequence effect in this study, data from period 1 only were used to evaluate these parameters.

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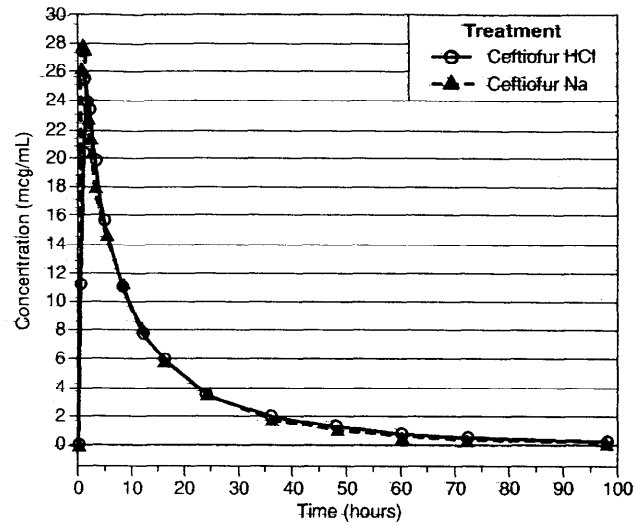
brand of ceftiofur hydrochloride sterile suspension

Figure 2. Swine plasma concentrations of ceftiofur and desfuroylceftiofur metabolites after EXCENEL RTU Sterile Suspension (ceftiofur hydrochloride sterile suspension, 50 mg/mL) or NAXCEL Sterile Powder (ceftiofur sodium sterile powder, 50 mg/mL) were administered intramuscularly at 2.27 mg ceftiofur equivalents/lb (5.0 mg/kg) BW.



Concentrations of total ceftiofur in the lungs of pigs administered radiolabeled ceftiofur at 2.27 or 3.41 mg ceftiofur equivalents/lb (5.0 or 7.5 mg/kg) BW 12 h after the last of three daily intramuscular injections at 24 h intervals averaged 3.66 and 5.63 µg/g.

Cattle: Ceftiofur administered as either ceftiofur sodium or ceftiofur hydrochloride is metabolized rapidly to desfuroylceftiofur, the primary metabolite. Administration of ceftiofur to cattle as either the sodium or hydrochloride salt provides effective concentrations of ceftiofur and desfuroylceftiofur metabolites in plasma above the MIC_{90} for the bovine respiratory disease (BRD) label pathogens *Pasteurella haemolytica (Mannheimia spp.), Pasteurella multocida* and *Haemophilus somnus* for at least 48 h. The relationship between plasma concentrations of ceftiofur and desfuroylceftiofur metabolites above the MIC_{90} in plasma and efficacy has not been established for the treatment of bovine interdigital necrobacillosis (foot rot) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

Comparative Bioavailability Summary

The comparability of plasma concentrations of ceftiofur following administration of ceftiofur hydrochloride sterile suspension (EXCENEL RTU Sterile Suspension) or ceftiofur sodium sterile solution (NAXCEL Sterile Powder) was demonstrated after intramuscular or subcutaneous administration of ceftiofur hydrochloride and intramuscular administration of ceftiofur sodium at 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW. See Table 2 and Figure 3.

Table 2. Cattle plasma concentrations and related parameters of ceftiofur and desfuroylceftiofur metabolites after EXCENEL RTU Sterile Suspension (ceftiofur hydrochloride sterile suspension, 50 mg/mL) administered intramuscularly or subcutaneously at 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW and NAXCEL Sterile Powder (ceftiofur sodium sterile powder, 50 mg/mL) administered intramuscularly at 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW.

	Ceftiofur hydrochloride		Ceftiofur sodium
	IM	SC	IM[1]
C_{max} µg/mL	11.0 ± 1.69	8.56 ± 1.89	14.4–16.5
t_{max} h	1–4 (range)	1–5 (range)	0.33–3.0
$t_{>0.2}$ h	60.5 ± 6.27	51.0 ± 6.53	50.7–50.9
$AUC_{0\text{-}LOQ}$ µg•h/mL	160 ± 30.7	95.4 ± 17.8	115–142
$t_{1/2}$ h	12.0 ± 2.63	11.5 ± 2.57	9.50–11.1
$C_{24\ h}$ µg/mL	1.47 ± 0.380	0.926 ± 0.257	0.86–1.16
$C_{48\ h}$ µg/mL	0.340 ± 0.110	0.271 ± 0.086	0.250–0.268

Definitions:

C_{max} – maximum concentration of drug in plasma in µg/mL

t_{max} – the time after initial injection to when C_{max} occurs, measured in hours

$t_{>0.2}$ – the time (in hours) plasma drug concentrations remain above 0.2 µg/mL

$AUC_{0\text{-}LOQ}$ – the area under the plasma drug concentration vs. time curve from time of injection to the limit of quantitation of the assay (0.15 µg/mL)

$t_{1/2}$ – the drug half life in plasma expressed in hours

$C_{24\ h}$ – the plasma drug concentration 24 h after administration

$C_{48\ h}$ – the plasma drug concentration 48 h after administration

[1] Values represent the separate means from each study.

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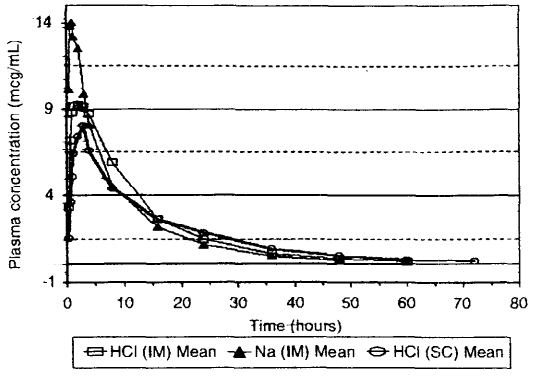
Figure 3. Cattle plasma concentrations of ceftiofur and desfuroylceftiofur metabolites after administration of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW of EXCENEL RTU Sterile Suspension (ceftiofur hydrochloride sterile suspension, 50 mg/mL) by intramuscular or subcutaneous injection or NAXCEL Sterile Powder (ceftiofur sodium sterile powder, 50 mg/mL) by intramuscular injection.



Total residues of ceftiofur were measured in the lungs of cattle administered radiolabeled ceftiofur at 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW at 24 h intervals for five consecutive days. Twelve h after the fifth injection of ceftiofur hydrochloride, total ceftiofur concentrations in the lung averaged 1.15 µg/g, while total ceftiofur concentrations in the lung 8 h after the fifth ceftiofur sodium injection averaged 1.18 µg/g.

MICROBIOLOGY

EXCENEL RTU Sterile Suspension is a ready to use formulation that contains the hydrochloride salt of ceftiofur, which is a broad spectrum cephalosporin antibiotic active against gram-positive and gram-negative bacteria including β-lactamase-producing strains. Like other cephalosporins, ceftiofur is bactericidal, *in vitro*, resulting in inhibition of cell wall synthesis.

In vitro activity has been demonstrated for ceftiofur against gram-positive organisms such as *Actinomyces pyogenes*, and other gram-negative organisms, such as *Escherichia coli* and *Salmonella typhimurium*. Ceftiofur was effective when tested in a variety of mouse disease models involving *Escherichia coli*, *Pasteurella multocida*, and *Salmonella typhimurium*. MIC_{90} values for ceftiofur against other pathogens are as follows: *Salmonella typhimurium* (98 isolates), 2.0 µg/mL; *Escherichia coli* (94 isolates), 1.0 µg/mL. The clinical significance of these findings is not known.

Swine: Studies with ceftiofur have demonstrated *in vitro* and *in vivo* activity against gram-negative pathogens, including *Actinobacillus (Haemophilus) pleuropneumoniae*, *Pasteurella multocida*, *Salmonella choleraesuis*, and the gram-positive pathogen *Streptococcus suis* type 2, all of which can be associated with swine bacterial respiratory disease – SRD (swine bacterial pneumonia). A summary of minimum inhibitory concentrations (MIC) for SRD pathogens is provided in Table 3.

Cattle: Studies with ceftiofur have demonstrated *in vitro* and *in vivo* activity against *Mannheimia* spp. (*Pasteurella haemolytica*), *Pasteurella multocida* and *Haemophilus somnus*, the three major pathogenic bacteria associated with bovine respiratory disease (BRD, pneumonia, shipping fever). A summary of MIC data for BRD pathogens is provided in Table 3.

Studies with ceftiofur have demonstrated *in vitro* and *in vivo* activity against *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*, two of the major pathogenic anaerobic bacteria associated with acute bovine interdigital necrobacillosis (foot rot, pododermatitis).

Antimicrobial Susceptibility

A summary of MIC data for swine (1993-1998) and cattle (1993-1994) pathogens is presented in Table 3. Clinical isolates were obtained in the United States. Testing followed NCCLS Guidelines (National Committee for Clinical Laboratory Standards).

Table 3. Minimum Inhibitory Concentrations for Ceftiofur Against SRD and BRD Clinical Isolates

Organism (# of strains tested)	MIC µg/mL Range	MIC_{90}	Date Tested
Swine			
Actinobacillus pleuropneumoniae (83)	≤0.03 – 0.06	≤0.03	1993
Pasteurella multocida (74)	≤0.03 – 0.06	≤0.03	1993
Streptococcus suis (94)	≤0.03 – 1.0	0.25	1993
Salmonella choleraesuis (50)	1.0 – 2.0	1.0	1993
beta-hemolytic *Streptococcus* spp. (24)	≤0.03 – 0.06	≤0.03	1993
Actinobacillus suis (77)	0.0019 – 0.0078	0.0078	1998
Haemophilus parasuis (76)	0.0039 – 0.25	0.06	1998

(continued)

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Organism (# of strains tested)	MIC µg/mL Range	MIC_{90}	Date Tested
Cattle			
Mannheimia spp. *(*Pasteurella haemolytica*)* (42)	≤0.003 – 0.03	0.015	1993
* *Pasteurella multocida* (48)	≤0.003 – 0.015	≤0.003	1993
* *Haemophilus somnus* (59)	no range	≤0.0019	1993
* *Fusobacterium necrophorum* (17)	≤0.06	≤0.06	1994
** *Bacteroides fragilis* group (29)	≤0.06 – >16.0	16.0	1994
** *Bacteroides* spp. non-fragilis group (12)	0.13 – >16.0	16.0	1994
** *Peptostreptococcus anaerobius* (12)	0.13 – 2.0	2.0	1994

* Clinical isolates supported by clinical data and indications for use.

** Clinical isolates not supported by clinical data, the clinical significance of these data is not known.

MIC_{90} Minimum inhibitory concentration for 90% of the isolates.

Based on the pharmacokinetic studies of ceftiofur in swine and cattle after a single intramuscular injection of 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) BW (swine) or 0.5 to 1.0 mg ceftiofur equivalents/lb (1.1 to 2.2 mg/kg) BW (cattle) and the MIC and disk (30 µg) diffusion data, the following breakpoints are recommended by NCCLS.

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 21	≤ 2.0	(S) Susceptible
18-20	4.0	(I) Intermediate
≤ 17	≥ 8.0	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" is a technical buffer zone and isolates falling into this category should be retested. Alternatively the organism may be successfully treated if the infection is in a body site where drug is physiologically concentrated. A report of "Resistant" indicates that the achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures[1] require the use of laboratory control organisms for both standardized diffusion techniques and standardized dilution techniques. The 30 µg ceftiofur sodium disk should give the following zone diameters and the ceftiofur sodium standard reference powder (or disk) should provide the following MIC values for the reference strain. Ceftiofur sodium disks or powder reference standard is appropriate for both ceftiofur salts.

QC Strain	MIC (µg/mL)	Disk Zone Diameter (mm)
E. coli ATCC 25922	0.25-1	24-30

CLINICAL EFFICACY

Cattle: In addition to demonstrating comparable plasma concentrations, the following clinical efficacy data are provided.

A clinical study was conducted to evaluate the efficacy of ceftiofur hydrochloride administered subcutaneously for the treatment of the bacterial component of BRD under natural field conditions. When uniform clinical signs of BRD were present, 60 cattle (111 to 207 kg) were randomly assigned to one of the following treatment groups: negative control or ceftiofur hydrochloride at 0.5 or 1.0 ceftiofur equivalents/lb (1.1 or 2.2 mg/kg) BW. Treatments were administered daily for three consecutive days. Cattle were evaluated daily and animals that died or were euthanatized were necropsied and the lung lesions scored. On Day 15, all surviving animals were euthanatized and necropsied and the lung lesions scored. Mortality rates were 65%, 10% and 5% for negative controls, 0.5 mg ceftiofur equivalents/lb and 1.0 mg ceftiofur equivalents/lb, (1.1 or 2.2 mg/kg) BW, respectively. Mortality rates for both ceftiofur hydrochloride treatment groups were lower than for negative controls ($P < 0.0001$). Rectal temperatures 24 h after third treatment were 104.0°F, 103.1°F and 102.8°F for negative controls, 0.5 mg/lb and 1.0 mg/lb (1.1 or 2.2 mg/kg) BW, respectively. The temperatures for both ceftiofur hydrochloride treatment groups were lower than the negative controls ($P \leq 0.05$). Ceftiofur hydrochloride administered subcutaneously for three consecutive days at 0.5 or 1.0 mg ceftiofur equivalents/lb (1.1 or 2.2 mg/kg) BW is an effective treatment for the bacterial component of BRD.

A three-location clinical field study was conducted to evaluate the efficacy of ceftiofur hydrochloride administered intramuscularly daily for three days or every other day (Days 1 and 3) for the treatment of the bacterial component of naturally occurring BRD. When uniform signs of BRD were present, 360 beef crossbred cattle were randomly assigned to one of the following treatment groups: negative control, ceftiofur sodium at 0.5 mg ceftiofur equivalents/lb (1.1 mg/kg) BW daily for three days, ceftiofur hydrochloride at 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW daily for three days, or ceftiofur hydrochloride at 1.0 mg ceftiofur equivalents/lb BW on Days 1 and 3 (every other day). All treatments were administered intramuscularly. All ceftiofur treatment groups (hydrochloride and sodium) and treatment regimens (every day and every other day) significantly ($P < 0.05$) reduced Day 4 rectal temperature as compared to the negative control. Clinical success on Days 10 and 28 and mortality to Day 28 were not different for the ceftiofur groups (hydrochloride and sodium) and treatment regimens (every day and every other day). The results of this study demonstrate that daily and every other day (Days 1 and 3) intramuscular administration of ceftiofur hydrochloride are effective treatment regimens for the bacterial component of BRD.

An eight location study was conducted under natural field conditions to evaluate the efficacy of ceftiofur hydrochloride for the treatment of acute post-partum metritis (0 to 14 days post-partum). When clinical signs of acute post-partum metritis (rectal temperature ≥ 103°F and fetid vaginal discharge) were observed, 361 lactating dairy cows were assigned randomly to treatment or negative control. Cattle were dosed either subcutaneously or intra-

Excenel® RTU

brand of ceftiofur hydrochloride sterile suspension

muscularly, daily for five consecutive days. On days 1, 5 and 9 after the last day of dose administration, cows were evaluated for clinical signs of acute post-partum metritis. A cure was defined as rectal temperature < 103°F and lack of fetid discharge. Cure rate for the 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW dose group was significantly improved relative to cure rate of the negative control on day 9. The results of this study demonstrate that ceftiofur hydrochloride administered daily for five consecutive days at a dose of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW is an effective treatment for acute post-partum metritis.

ANIMAL SAFETY

Swine: Results from a five-day tolerance study in normal feeder pigs indicated that ceftiofur sodium was well tolerated when administered at 57 mg ceftiofur equivalents/lb (125 mg/kg) (more than 25 times the highest recommended daily dosage of 2.27 mg/lb (5.0 mg/kg)) BW for five consecutive days. Ceftiofur administered intramuscularly to pigs produced no overt adverse signs of toxicity.

To determine the safety margin in swine, a safety-toxicity study was conducted. Five barrows and five gilts per group were administered ceftiofur sodium intramuscularly at 0, 2.27, 6.81 and 11.36 mg ceftiofur equivalents/lb (0, 5, 15, 25 mg/kg) BW for 15 days. This is 0, 1, 3 and 5 times the highest recommended dose of 2.27 mg/lb (5.0 mg/kg) BW/day and 5 times the recommended treatment length of 3 days. There were no adverse systemic effects observed, indicating that ceftiofur has a wide margin of safety when injected intramuscularly into feeder pigs at the highest recommended dose of 2.27 mg ceftiofur equivalents/lb (5.0 mg/kg) BW daily for 3 days or at levels up to 5 times the highest recommended dose for 5 times the recommended length of treatment.

A separate study evaluated the injection site tissue tolerance of EXCENEL RTU (ceftiofur hydrochloride) in swine when administered intramuscularly in the neck at 1.36 and 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) BW. Animals were necropsied at intervals to permit evaluations at 12 h, and 3, 5, 7, 9, 11, 15, 20, and 25 days after last injection. Injection sites were evaluated grossly at necropsy. No apparent changes (swelling or inflammation) were observed clinically after 12 h post-injection. Areas of discoloration associated with the injection site were observed at time periods less than 11 days after last injection.

Cattle: Results from a five-day tolerance study in feeder calves indicated that ceftiofur sodium was well tolerated at 25 times (25 mg ceftiofur equivalents/lb (55 mg/kg) BW) the highest recommended dose of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW for five consecutive days. Ceftiofur administered intramuscularly had no adverse systemic effects.

In a 15-day safety/toxicity study, five steer and five heifer calves per group were administered ceftiofur sodium intramuscularly at 0 (vehicle control), 1, 3, 5 and 10 times the highest recommended dose of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW to determine the safety factor. There were no adverse systemic effects indicating that ceftiofur sodium has a wide margin of safety when injected intramuscularly into the feeder calves at 10 times (10 mg ceftiofur equivalents/lb (22 mg/kg) BW) the recommended dose for three times (15 days) the recommended length of treatment of three to five days. Local tissue tolerance to intramuscular injection of ceftiofur hydrochloride was evaluated in the following study.

Results from a tissue tolerance study indicated that ceftiofur hydrochloride was well tolerated and produced no systemic toxicity in cattle when administered intramuscularly in the neck and rear leg at a dose of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW at each injection site. This represents a total dose per animal of 2.0 mg ceftiofur equivalents/lb (4.4 mg/kg) BW. Clinically noted changes (local swelling) at injection sites in the neck were very infrequent (2/48 sites) whereas noted changes in rear leg sites were more frequent (21/48 sites). These changes in the rear leg injection sites were generally evident on the day following injection and lasted from 1 to 11 days. At necropsy, injection sites were recognized by discoloration of the subcutaneous tissues and muscle that resolved in approximately 7 to 15 days in the neck and 19 to 28 days in the rear leg.

Results from another tissue tolerance study indicated that ceftiofur hydrochloride was well tolerated and produced no systemic toxicity to cattle when administered subcutaneously at 0.5 or 1.0 mg ceftiofur equivalents/lb (1.1 or 2.2 mg/kg) BW at 24 h intervals for 5 days. Mild and usually transient, clinically visible or palpable reactions (local swelling) were localized at the injection site. At necropsy, injection sites were routinely recognized by edema, limited increase in thickness and color changes of the subcutaneous tissue and/or facial surface of underlying muscle. The facial surface of the muscle was visibly affected in most cases through 9.5 days after injection. Underlying muscle mass was not involved. There were no apparent differences in tissue response to administration of ceftiofur hydrochloride at 0.5 or 1.0 mg ceftiofur equivalents/lb (1.1 or 2.2 mg/kg) BW.

INDICATIONS

Swine: EXCENEL RTU Sterile Suspension is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis* and *Streptococcus suis* type 2.

Cattle: EXCENEL RTU Sterile Suspension is indicated for treatment of the following bacterial diseases:

— Bovine respiratory disease (BRD, shipping fever, pneumonia) associated with *Mannheimia* spp. (*Pasteurella haemolytica*), *Pasteurella multocida* and *Haemophilus somnus*.

— Acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus*.

— Acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur.

CONTRAINDICATIONS

As with all drugs, the use of EXCENEL RTU Sterile Suspension is contraindicated in animals previously found to be hypersensitive to the drug.

DOSAGE AND ADMINISTRATION

Swine: Administer intramuscularly at a dosage of 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) BW (1 mL of sterile suspension per 22 to 37 lb BW). Treatment should be repeated at 24 h intervals for a total of three consecutive days.

Cattle:

— For bovine respiratory disease and acute bovine interdigital necrobacillosis: administer by intramuscular or subcutaneous administration at the dosage of 0.5 to 1.0 mg ceftiofur equivalents/lb (1.1 to 2.2 mg/kg) BW (1 to 2 mL sterile suspension per 100 lb BW). Administer daily at 24 h intervals for a total of three consecutive days. Additional treatments may be administered on Days 4 and 5 for animals which do not show a satisfactory response (not recovered) after the initial three treatments. In addition, for BRD only, administer intramuscularly or subcutaneously 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW every other day on Days 1 and 3 (48 h interval). Do not inject more than 15 mL per injection site.

Selection of dosage level (0.5 to 1.0 mg/lb) and regimen/duration (daily or every other day for BRD only) should be based on an assessment of the severity of disease, pathogen susceptibility and clinical response.

— For acute post-partum metritis: administer by intramuscular or subcutaneous administration at the dosage of 1.0 mg ceftiofur equivalents/lb (2.2 mg/kg) BW (2 mL sterile suspension per 100 lb BW). Administer at 24 h intervals for five consecutive days. Do not inject more than 15 mL per injection site.

Shake well before using.

WARNINGS

NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth, and clothing.

Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention.

The material safety data sheet contains more detailed occupational safety information. To report adverse effects in users, to obtain more information or obtain a material safety data sheet, call 1-800-253-8600.

RESIDUE WARNINGS: No pre-slaughter drug withdrawal interval is required when this product is used in swine. Treated cattle must not be slaughtered for 48 hours (2 days) following last treatment because unsafe levels of drug remain at the injection sites. No milk discard time is required when this product is used according to label directions. Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk. A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal.

PRECAUTIONS

Swine: Areas of discoloration associated with the injection site at time periods of 11 days or less may result in trim-out of edible tissues at slaughter. The safety of ceftiofur has not been demonstrated for pregnant swine or swine intended for breeding.

Cattle: Following intramuscular or subcutaneous administration in the neck, areas of discoloration at the site may persist beyond 11 days resulting in trim loss of edible tissues at slaughter. Following intramuscular administration in the rear leg, areas of discoloration at the injection site may persist beyond 28 days resulting in trim loss of edible tissues at slaughter.

STORAGE CONDITIONS

Store at controlled room temperature 20° to 25° C (68° to 77° F) [see USP]. Shake well before using. Protect from freezing.

HOW SUPPLIED

EXCENEL RTU Sterile Suspension is available in the following package size:

100 mL vial NDC 0009-3504-03

[1] National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Proposed Standard. NCCLS Document M31-P (ISBN 1-56238-258-6). NCCLS, 771 East Lancaster Avenue, Villanova, Pennsylvania 19085, 1994.

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Pharmacia & Upjohn Company • Kalamazoo, MI 49001, USA

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